[Frontiers in Bioscience S1, 125-131, June 1, 2009]

The role of FGF-2 in renal fibrogenesis

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1. ABSTRACT

Basic fibroblast growth factor (FGF-2) is a pleiotropic cytokine which exerts its effects via four different high affinity receptors (FGFR-1 to -4) which function as protein tyrosine kinases. In the kidney, FGF-2 is expressed in epithelial cells already during fetal development. During later stages, expression of the cytokine can be found in distal tubular epithelial cells, glomerular cells and few interstitial cells. Expression in fibroblasts is robustly upregulated in chronic kidney scarring pointing to an important role in fibrogenesis. Functional studies have demonstrated that FGF-2 exerts mainly proliferative effects on a variety of renal cell types. In regard to fibrogenesis, the expression and induction of proliferation in interstitial fibroblasts may be the most important function. FGF-2 is one of the key factors contributing to autocrine fibroblast proliferation in post-inflammatory matrix synthesis. In addition, FGF-2 facilitates epithelial to mesenchymal transition of tubular epithelial cells contributing early to an increase of matrix producing cells. However, the cytokine does not contribute directly to extracellular matrix synthesis. Still, many aspects of FGF-2 in renal fibrogenesis remains to be evaluated.

2. INTRODUCTION

Historically, the relationship between the tubulointerstitial compartment and renal function in glomerular disease was described as early as in 1844 in Germany (1) and in 1846 in England (2): in both observations, tubulointerstitial scarring was found to correlate better with the disease process than glomerular lesions. However, in subsequent years, these observations have been forgotten and tubulointerstitial changes observed in glomerulopathies were considered non-relevant. That changed in 1953 when the importance of the tubulointerstitial space for renal function was rediscovered by Spühler and Zollinger, albeit in patients with primary interstitial nephritis (3). Subsequently, in 1958, Hutt and coworkers observed a relationship between tubulointerstitial lesions and renal function in 15 patients with acute glomerulonephritis (4). This relationship was confirmed in patients with different types of glomerulopathy and chronic tubulointerstitial disease by Adalbert Bohles group at the University of Tuebingen, Germany. Studies on mesangioproliferative, membranous, focal-sclerosing, and membranoproliferative glomerulonephritis showed convincingly a robust

correlation between the morphometrically measured interstitial volume and serum creatinine (reviewed in (5)). Moreover, the extent of interstitial inflammation and fibrosis were reliable predictors of renal function 5 or more years later (6). Similar observations were made by the same group also in secondary glomerulopathies such as diabetic glomerulosclerosis (7) and glomerular amyloidosis (8). These findings have been subsequently confirmed by many other groups (reviewed in (9)). All in all, the overwhelming evidence for a decisive role of tubulointerstitial involvement in the deterioration of renal function and the progression to chronic renal failure is not surprising given the fact that the tubulointerstitial space occupies approximately 80 per cent of the renal volume (10).

3. RENAL FIBROGENESIS

It has traditionally been tempting to compare the process and result of tissue fibrosis to wound healing in the skin. There is great heterogeneity in outcome in the latter; fetal wounding, for example, produces no scar, adult wounding results in an appropriate closure that contracts and minimizes over time or, in some cases, scars enlarge to produce keloids (11). Like wound healing in the skin, three phases of fibrogenesis can be distinguished in the kidney; induction, inflammatory, and post-inflammatory phases (12). There is a certain degree of variability in these phases which may account for heterogeneous outcomes. Renal fibrogenesis differs from typical wound healing, however, in that true resolution is rare. Instead, matrix synthesis continues with insidious destruction of normal organ architecture and eventual loss of function, interestingly enough this process may continue despite resolution of primary inflammation (13).

4. INDUCTION OF RENAL FIBROGENESIS AND EFFECTOR CELLS

Renal fibrogenesis commences with the induction phase. This phase is critical for the subsequent accumulation of matrix proteins and is characterized by the influx of infiltrating mononuclear cells. Interstitial infiltrates can be found in almost all forms of primary or secondary glomerular disease (14), with only few exceptions (15). Infiltrating mononuclear cells are composed mainly of monocytes/macrophages and lymphocytes, predominantly T-lymphocytes (16). After inflammatory cells infiltrate renal tissue, one begins to see activation and proliferation of fibroblasts. So-called myofibroblasts (the name is due to the de-novo expression of alphasmooth muscle actin in these cells whose expression is normally restricted to vascular smooth muscle cells) are the key (though not exclusive) effector cells in renal fibrogenesis (17). The formation of myofibroblasts may occur via an intermediate form, the so-called “protomyofibroblast” characterized by the acquisition of contractile stress fibers (18). In the kidney, myofibroblasts are derived mainly from activation of resident interstitial fibroblasts, albeit differentiation processes of periadventitial cells, bone marrow derived cells or tubular epithelial cells may contribute as well (19). The differentiation process of tubular epithelial cells refers to epithelial to mesenchymal transition (EMT) which was first described by our group in 1995 by cloning of FSP1, a member of the S100 protein family (20). FSP1 expression is constitutive in tissue fibroblasts under physiologic conditions (20). In a mouse model of rapidly progressive fibrosis (the model of unilateral ureteral obstruction), 36 per cent of interstitial matrix producing cells were of tubular origin, i.e. generated by EMT as identified by genetically tagged proximal tubular epithelial cells which migrated into the interstitium and expressed de novo mesenchymal marker proteins (21). However, the relative contribution of EMT to myofibroblast formation may be smaller in fibrotic disease with slower progression rates. All in all, there is a remarkable variability in the results of studies that evaluated the origin of renal fibroblasts. A possible explanation for such a discrepancy is that fibroblast recruitment may occur disease-specific (19). For example, EMT could not be observed in a model of overload proteinuria (22). Conversely, the specific significance of EMT for the progression of renal disease was shown very convincingly by Yang *et al.* who demonstrated that EMT was critical for the progression of renal disease in the UUO model compared to the tissue plasminogen activator deficient mice (23).

5. FGF-2

Gospodarowicz and colleagues described as early as 1974 the mitogenic effects of bovine pituitary extract on 3T3 fibroblasts which later was determined to be FGF-2 (24). Due to different translation start sites, five different isoforms of FGF-2 can be distinguished of which only the 18 kD isoform gets secreted. It exerts its effects via four different high affinity receptors (FGFR-1 to –4). These FGFRs function as protein tyrosine kinases and regulate a wide variety of cellular processes (reviewed in (25)). Additionally, various heparin sulfate proteoglycans serve as low affinity receptors. Moreover, recently, non-tyrosine kinase receptors have recently been implicated in FGF-2 signalling (26). Unlike most other polypeptide growth factors, FGF-2 does not have a leader sequence and the mechanisms for its release are still controversial. However, it was shown that injured cells do release FGF-2 into the surrounding tissue (27) and the cytokine may be secreted by viable cells as well (28).

FGFs in general are pleiotropic molecules capable of affecting a variety of cell types and FGF-2 is no exception (29). FGF-2 has an important role in angiogenesis since it stimulates vascular endothelial growth factor (VEGF) expression in endothelial and stromal cells (30). In addition, FGF signaling controls the VEGF receptor 2 signaling responsiveness (29). However, clinical trials applying angiogenic growth factors in patients with ischemic heart disease have failed to demonstrate any therapeutic efficacy (31).

5. 1. FGF-2 in the kidney

FGF-2 expression in the kidney was first described in 1985 when Baird and colleagues isolated the cytokine from whole bovine kidneys (32). In the human fetal kidney, FGF-2 expression is detectable mainly in

epithelial cells in different stages of differentiation (33). Takeuchi *et al.* and Floege *et al.* examined the expression of FGF-2 in adult kidneys more closely and described expression in some tubules, the interstitial space, but mainly in Bowman's capsule, the mesangial space and in the vasculature (34, 35). However, these findings could not be confirmed by all investigators probably due to the use of different affinity antibodies (36). With the use of four different antibodies, Floege and colleagues localized FGF-2 expression in normal human kidneys most consistently to vascular smooth muscle and distal tubular epithelial cells (37). Our own studies in human kidneys demonstrated that FGF-2 is expressed not only in glomerular and vascular cells but also in selected interstitial fibroblasts (38). *In situ* hybridization studies and western blot analyses of fibroblasts confirmed these results.

FGF-2 is mitogenic for many renal cell types including glomerular endothelial (39) and glomerular epithelial cells (34) but also for mesangial (40) and proximal tubule cells (41). Functionally, FGF-2 may augment podocyte injury and glomerulosclerosis in rats induced with a model of membranous nephropathy (42). In addition, chronic infusion of FGF-2 resulted in glomerulosclerosis and interstitial fibrosis in rats (43). Both studies point to a role of FGF-2 in renal sclerosing disease. More recently, Li *et al.* demonstrated that FGF-2 may be involved in renal cyst formation by overexpression of human FGF-2 in newborn mice (44). Our group did study the expression of FGF-2 in human diabetic nephropathy and found a robust upregulation within the tubulointerstitium but not within the glomerulus in kidneys with diabetic renal involvement (Vasko *et al.*, submitted).

Conversely, to these potential pro-fibrotic effects, there is no study analyzing the effects of FGF-2 on renal angiogenesis.

5. 2. Early role of FGF-2 in renal fibrogenesis

How is FGF-2 (basic fibroblast growth factor) involved in the induction phase of renal fibrogenesis? We do not know exactly since no study has analyzed the expression of the cytokine carefully in a progressive animal model. Studying human kidney biopsies with variable degrees of interstitial inflammation and interstitial scarring, FGF-2 expression was robustly upregulated in interstitial and tubular epithelial cells by immunohistochemistry and in-situ hybridization (38). Some of the interstitial cells may have been inflammatory infiltrating cells. Moreover, studying the functional effects on human renal fibroblasts, we found induction of proliferation in primary cortical fibroblasts and promotion of the expression of alpha-smooth muscle actin in these cells indicating activation of these cells within the induction phase (38). Ray *et al.* examined FGF-2 expression in a transgenic mouse model of HIV nephropathy and found that interstitial FGF-2 staining was increased and colocalized with extracellular matrix (45). FGF-2 expression may be induced in inflammatory vascular processes as well as was shown by the same group studying children with hemolytic uremic syndrome (46). Finally, Stein-Oakley and colleagues described increased FGF-2 expression in the tubulointerstitial space from kidneys with focal segmental glomerulosclerosis and IgA nephropathy (47), though again, the exact time course was not analyzed.

In regard to EMT, the effects of FGF-2 were examined by our group a number of years ago (48). One key feature of EMT is increased cell motility as a characteristic property of mesenchymal cells. In our studies, FGF-2 induced cell motility dose dependently across a tubular basement membrane in two tubular cell lines. In addition, the expression of the mesenchymal marker proteins vimentin and FSP1 was induced by incubation with FGF-2, whereas cytokeratin expression was downregulated by immunofluorescence. These effects were most notable in the distal tubular epithelial cell line and were confirmed by immunoblot analyses. Furthermore, FGF-2 stimulated FSP1 and decreased E-cadherin promoter activities in stably tranfected tubular epithelial cells. FGF-2 also induced intracellular fibronectin synthesis. Conversely, fibronectin secretion could only be stimulated by TGF-ß1, not by FGF-2 alone. The tubular basement membrane is a barrier which often prevents the migration of tubular epithelial cells into the tubulointerstitial space. Since it is composed mainly of type IV collagen, the appropriate matrix degrading enzymes (e.g. matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9) are required for degradation of the tubular basement membrane. Thus, zymographic analyses demonstrated that FGF-2 induced MMP-2 activity by 2.6-fold and MMP-9 activity by 2.4-fold, providing a putative mechanism for basement membrane disintegration and migratory access of transforming epithelium to the interstitium.

Figure 1 illustrates the effects of FGF-2 on EMT. Similar effects may be induced by other profibrotic cytokines such as TGF-ß1 (transforming growth factor) or Oncostatin M (49), to name only a few.

5.3 . FGF-2 in the inflammatory phase of renal fibrogenesis

During the phase of inflammatory matrix synthesis, fibroblasts are stimulated mainly by cytokines from infiltrating inflammatory cells as well as from resident renal cells. Several cytokines play key roles in that process including angiotensin II, transforming growth factor beta (TGF-beta), connective tissue growth factor (CTGF), epidermal growth (EGF), and platelet derived growth factor growth factor (PDGF). Certainly, TGF-ß1 is one of most important profibrotic cytokines.

The role of FGF-2 in the inflammatory phase of renal fibrogenesis is probably much less prominent. As was shown by our group, FGF-2 has only marginal effects on the synthesis of extracellular matrix proteins in renal fibroblasts (38). However, our group was able to demonstrate that TGF-ß1 induces FGF-2 synthesis on the mRNA and protein levels robustly and may result in the release of preformed FGF-2. Furthermore, we demonstrated that TGF-ß1 promotes proliferation in

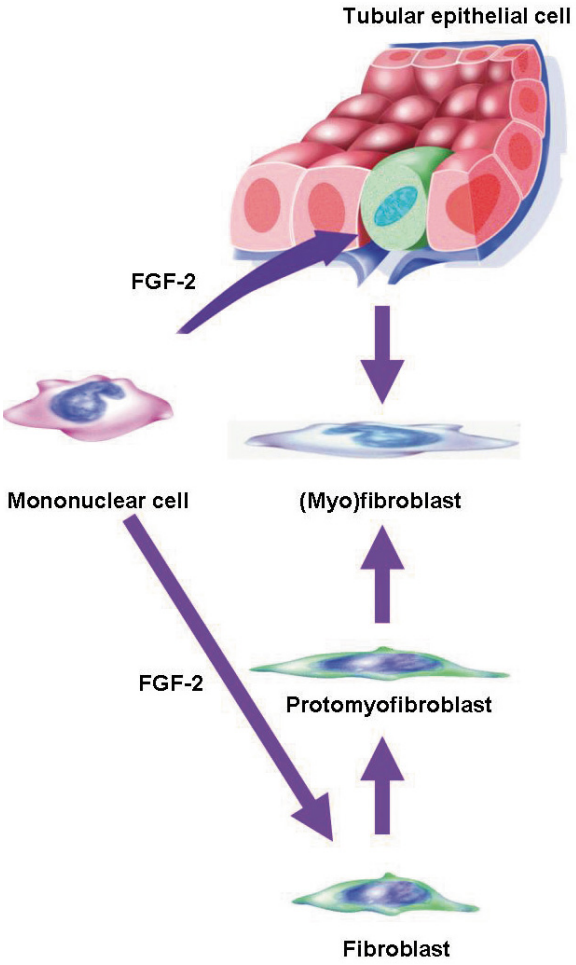

Figure 1. Simplified schematic of the effects of FGF-2 on the process of epithelial mesenchymal transition and on the activation process of fibroblasts to myofibroblasts via the intermediate form of the protomyofibroblast. Please note that whereas FGF-2 does induce these differentiation processes, it does not stimulate secretion of extracellular matrix.

medullary and cortical fibroblasts and that this effect is mediated mainly by induction of FGF-2 (50).

5.4 . Postinflammatory phase and FGF-2

The phase of postinflammatory matrix synthesis distinguishes tissue fibrogenesis from typical wound healing where resolution is expected. In this phase, the primary inflammatory process is often confined to limited areas. However, despite apparent resolution of inflammation, interstitial matrix synthesis and deposition continue. There are several possibilities how fibrogenesis may continue during that phase: First, stimulation by the few remaining interstitial infiltrates is strong enough to result in persisting fibroblast activity. Second, autocrine loops in activated fibroblast may result in autonomous stimulation of these cells. Lonnemann *et al.*, for example, observed that IL-1 secreted by fibrotic kidney derived fibroblasts led to a mitogenic response and autocrine stimulation of its own secretion (51). Our own studies emphasize the role of FGF-2 in autocrine fibroblast proliferation since neutralization of the cytokine caused inhibition of basal proliferation (38). Furthermore, as indicated above, we were able to demonstrate that TGF-beta1 induced synthesis and secretion of FGF-2 from cortical fibroblasts (13). A third mechanism of postinflammatory matrix synthesis is the interaction between tubular epithelial cells and fibroblasts. Again, FGF-2 seems to be involved in that process. Phillips *et al.* showed that FGF-2 may stimulate release of latent TGF-beta1 from proximal tubule cells and indicate the presence of another positive feed-back loop (52). A fourth very interesting mechanism was recently described by Wallach-Dayan *et al.* in pulmonary fibrosis (53). These authors found an overexpression of the Fas ligand (FasL) in myofibroblasts from fibrotic lungs allowing these cells to escape immune surveillance and to proliferate. Of course, these findings will have to be confirmed for the kidney (54).

Figure 2 summarizes the possible pathogenetic mechanisms of postinflammatory matrix synthesis focusing on FGF-2. This phase is probably characterized by the existence of several autocrine loops. The critical role of FGF-2 and TGF-ß1 in post-inflammatory matrix synthesis is corroborated by studies on fetal wound healing. During fetal wound healing no scarring can be observed. However, in post-fetal wound healing scarring commonly occurs. As was demonstrated in a nice series of experiments, one of the major differences besides the organization of collagen fibers between fetal and post-fetal wound healing is the expression of the two cytokines FGF-2 and TGF-ß1 which can be easily detected in post-fetal (scarring) but not in fetal (non-scarring) wounds (55, 56).

5.5. FGF-2 in non-renal fibrosis

Besides the kidney, FGF-2 has been implicated in the pathogenesis of skin, liver und pulmonary fibrosis. Gonzalez and colleagues described the association of FGF-2 expression with proliferative fibrogenesis in patients with Dupuytren's contracture (57). Charlotte *et al.*, for example, found increased expression of FGF-2 in carbon tetrachloride induced liver fibrosis (58). That study confirmed already an expression of the cytokine in liver myofibroblasts. Yu and colleagues examined the effects of FGF-1 and FGF-2 double knock-out mice and found that liver fibrosis was much less severe compared to regular control mice expressing both cytokines (59). This study again points to a profibrogenic role of FGF-2 though it is difficult to discern the effects of FGF-2 from FGF-1 using this approach. However, there are also some reports claiming a beneficial effect of FGF-2 on fibrogenesis. For example, Ishikawa and colleagues treated carbon-tetrachloride induced liver fibrosis in mice with a combination of bone marrow transplantation and FGF-2 and found that the combination improved matrix deposition (60). Interestingly, Akasaka *et al.* described a proapoptotic effect of FGF-2 on dermal fibroblasts and an inhibition of alpha-smooth muscle actin expression (61), thus, opposite effects to those described in the kidney. The potential pro-fibrotic effects of FGF-2 are corroborated by studies using

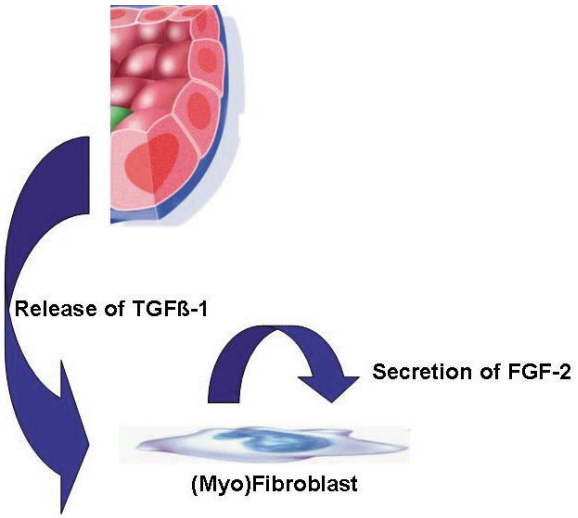

Figure 2. Schematic of the possible mechanisms of post-inflammatory matrix synthesis. Autocrine and paracrine loops of (myo)fibroblasts and tubular epithelial cells may be involved in continous fibroblast proliferation responsible in part for post-inflammatory matrix synthesis.

FGF deficient mice which display (mild) delays in wound healing (62).

6. CONCLUSION AND PERSPECTIVE

There is little doubt that FGF-2 is a profibrotic cytokine in the kidney exerting mainly proproliferative effects on cortical fibroblasts and facilitating EMT. In addition, robust upregulation of expression particularly in the tubulointerstitium has been described in correlation with scarring. However, to date no studies have been performed in FGF-2 deficient mice and no studies have used complete neutralization of the cytokine studying fibrogenesis. However, vaccination therapies against FGF-2 have been developed with some success in animal studies (63) whereas clinical studies so far have failed due probably to redundancy of the FGF system. In addition, some studies in non-renal tissue point to certain anti-fibrotic effects and certainly induction of angiogenesis may have potential beneficial effects on the course of chronic progressive renal failure. Thus, the effects of FGF-2 may vary depending on the time course and maybe even depending on the model used. Further studies are urgently needed in order to better define the role of FGF-2 in renal fibrogenesis.

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Key Words: FGF, Fibroblast growth factor, Angiogenesis, Kidney, Review

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